

REVIEW

EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide

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ABSTRACT

The EULAR Sjögren's syndrome (SS) disease activity index (ESSDAI) is a systemic disease activity index that was designed to measure disease activity in patients with primary SS. With the growing use of the ESSDAI, some domains appear to be more challenging to rate than others. The ESSDAI is now in use as a gold standard to measure disease activity in clinical studies, and as an outcome measure, even a primary outcome measure, in current randomised clinical trials. Therefore, ensuring an accurate and reproducible rating of each domain, by providing a more detailed definition of each domain, has emerged as an urgent need. The purpose of the present article is to provide a user guide for the ESSDAI. This guide provides definitions and precisions on the rating of each domain. It also includes some minor improvement of the score to integrate advance in knowledge of disease manifestations. This user guide may help clinicians to use the ESSDAI, and increase the reliability of rating and consequently of the ability to detect true changes over time. This better appraisal of ESSDAI items, along with the recent definition of disease activity levels and minimal clinically important change, will improve the assessment of patients with primary SS and facilitate the demonstration of effectiveness of treatment for patients with primary SS.

INTRODUCTION

With the growing interest in conducting clinical trials in primary Sjögren's syndrome (SS), having specific and valid outcome measures became a necessity. For that purpose, an international collaboration was set up to develop and validate the EULAR Sjögren's syndrome disease activity index (ESSDAI)¹ and EULAR Sjögren's syndrome patient reported index (ESSPRI).²

The ESSDAI is a systemic disease activity index that was generated in 2009. This score has been developed by consensus of a large group of worldwide experts from European and North American countries, supported by the EULAR (project code CLI 010).¹ It includes 12 domains (ie, organ systems: cutaneous, respiratory, renal, articular, muscular,

Key messages

- The EULAR Sjögren's syndrome (SS) disease activity index (ESSDAI) is a clinical index that measures disease activity in primary Sjögren's syndrome.
- ESSDAI is validated and used in most clinical studies and ongoing randomised controlled trials.
- This glossary provides detailed definitions of each item; useful in clinical trials to ensure reliability.

peripheral nervous system (PNS), central nervous system (CNS), haematological, glandular, constitutional, lymphadenopathic, biological). The ESSDAI includes organ-by-organ definitions that were agreed on by a large number of experts. Each domain is divided into 3–4 levels of activity. Definition of each activity level is provided by a detailed description of what should be considered in that item. The aim was to obtain a standardised instrument for the homogenous evaluation of systemic activity in order for the ESSDAI to be used as outcome criteria to evaluate primary SS in clinical trials as well as daily practice.

This tool has been validated in a large independent cohort and has been shown to have a high content validity, to be highly reproducible and to be able to detect change.^{3,4}

In the past few years, the use of this tool has become more and more prevalent,^{5–7} particularly in the context of randomised controlled trials (RCTs).^{8–10} With the growing use of the ESSDAI, some domains appeared to be more challenging to rate than others. In the context of an RCT, ensuring a more accurate and reproducible rating of each domain, by providing a more detailed definition of each domain, emerged as an urgent need. The purpose of the present article is to provide a user guide for clinicians who use the ESSDAI to help them to measure disease activity and to ensure the best accuracy of this measure for its use in RCTs as well as in clinical practice. For

each of the ESSDAI domains, we will focus on the potentially difficult items.

METHODS

This glossary results from an initiative of the steering committee of the EULAR Sjögren's task force collaborative group (project code CLI 010). This group of 10 physician experts in SS (HB, SJB, TD, J-EG, XM, MR-C, RS, ET, AT and CV) and a clinical epidemiologist (PR), has led the development of the ESSDAI. To develop the ESSDAI, we also contacted one collaborator of a member of the steering committee (SC) who has vast experience in the use of the ESSDAI in the clinical and research setting (PB-Z).

Based on their experience in the use of the ESSDAI, three members of the SC (SJB, XM and RS) identified difficulties in rating ESSDAI items. They prepared a draft for a glossary that aimed to clarify these difficult ratings. This proposal was submitted to other experts of the SC. They were asked to suggest any changes they wanted made. Their suggestions were submitted for the approval of all the SC members by email. The modifications were integrated until all members of the SC agreed on a final version.

ESSDAI domains glossary

First, two important points have been emphasised by the SC to be considered by physicians who use the ESSDAI:

1. The ESSDAI has been developed for patients with **primary** SS. Therefore, other differential diagnoses should be ruled out. When the ESSDAI is used, it should be with the assurance that the signs and symptoms are related to primary SS and not to an underlying and/or associated disease. Likewise, patients with primary SS may have concomitant illnesses that can mimic SS symptoms and organ involvement, which should be taken into account.
2. When assessing disease activity of an individual patient, the physician has to keep in mind that he/she has to exclude damage features that are irreversible. Therefore, for each single domain, the long-lasting fixed features (stable for at least 12 months) should be scored as 0.

Constitutional domain

Domain	Activity level	Description
Constitutional <i>Exclusion of fever of infectious origin and voluntary weight loss</i>	No=0	Absence of the following symptoms
	Low=3	Mild or intermittent fever (37.5–38.5°C)/night sweats and/or involuntary weight loss of 5–10% of body weight
	Moderate=6	Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight

The rating of this domain should take into account the following comments:

Fever and night sweats: The presence of fever (measured by the patient or the physician using a thermometer) and night sweats is based on patient responses following direct questioning 'Have you had fevers or night sweats in the past 4 weeks?'

If the fever is regularly (at least twice a week) >38.5°C or if the night sweats wet the nightclothes, score as moderate activity, else in presence of milder constitutional symptoms score as low activity.

Symptoms that are thought to be due to causes other than SS, for example, menopause, concomitant infection or neoplasia, should be scored as 0.

Weight loss: Weight loss should be recent to be taken into account (within the past 12 weeks). Where the weight loss is intentional or due to a concomitant illness, it should be scored as 0.

Constitutional symptoms related to lymphoma should be scored in the constitutional domain in addition to the scoring of lymphoma.

Lymphadenopathy and lymphoma domain

Domain	Activity level	Description
Lymphadenopathy and lymphoma <i>Exclusion of infection</i>	No=0	Absence of the following features
	Low=4	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate=8	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High=12	Current malignant B-cell proliferative disorder

To be clearer, we added 'and lymphoma' in the title of the domain.

The rating of this domain should take in account the following comments:

Lymphadenopathy or splenomegaly: If there is no significant lymph node or splenomegaly at the clinical examination, no other examination is requested. If there are some clinical abnormalities, and if an ultrasound or CT scan has been performed, these data will be used for scoring, else clinical abnormalities should be used for scoring.

Lymphadenopathies that are thought to be due to causes other than SS, for example, to a concomitant infection, should be scored as 0.

Multiple myeloma is not to be taken into account.

Domain	Activity level	Description
Glandular <i>Exclusion of stone or infection</i>	No=0	Absence of glandular swelling
	Low=2	Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular (≤ 2 cm) or lachrymal swelling (≤ 1 cm)
	Moderate=4	Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular (> 2 cm) or lachrymal swelling (> 1 cm)

In case of gland enlargement due only to lymphoma, lymphoma will be scored in the ‘Lymphadenopathy and lymphoma’ domain but not in the glandular domain. If the gland is enlarged independently from lymphoma, or if the contralateral gland or other salivary glands are enlarged, both domains should be scored.

Domain	Activity level	Description
Articular <i>Exclusion of osteoarthritis</i>	No=0	Absence of currently active articular involvement
	Low=2	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate=4	1–5 (of 28 total count) synovitis
	High=6	≥6 (of 28 total count) synovitis

Domain	Activity level	Description
Cutaneous <i>Rate as 'No activity' stable long-lasting features related to damage</i>	No=0	Absence of currently active cutaneous involvement
	Low=3	Erythema multiforma
	Moderate=6	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High=9	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis

The rating of this domain should take into account the following comments:

Erythema multiforma: are typical targets, or raised, oedematous papules distributed acraly; involvement of mucous membranes is possible.

Subacute cutaneous lupus erythematosus (SCLE) is characterised by two forms, including papulosquamous lesions and annular lesions that develop in sun-exposed areas, including the upper back, shoulders, extensor arms, neck and upper torso, while the face is usually spared.

Cutaneous vasculitis should include purpura, maculopapular rash or urticarial rash. Lesions other than purpura and supposedly due to vasculitis such as isolated urticarial or macular rash of vasculitic origin should be confirmed (by histology and/or the presence of cryoglobulins) at least once in patient history.

Cutaneous vasculitic activity is classified according to the cutaneous extension as moderate activity (if limited to <18% of the body surface area) or high activity (if extended to ≥18% of the body surface area or if showing presence of ulcers). The body surface area involved is evaluated according to [figure 1](#).

If a skin biopsy has been performed this should be used. Otherwise, scoring is based on clinical examination by a medical professional with suitable training and experience.

Cutaneous rash due to infections, drug reaction or neoplasia should be excluded. In case of SCLE, underlying SLE should be excluded.

Pulmonary domain

Domain	Activity level	Description
Pulmonary Rate as 'No activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)	No=0	Absence of currently active pulmonary involvement
	Low=5	Persistent cough due to bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: no breathlessness and normal lung function test
	Moderate=10	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NYHA II) or abnormal lung function tests restricted to: 70% >DL _{CO} ≥40% or 80% >FVC≥60%
	High=15	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NYHA III, IV) or with abnormal lung function tests: DL _{CO} <40% or FVC <60%
FVC, forced vital capacity; HRCT, high-resolution CT; NYHA, New York Heart Association.		

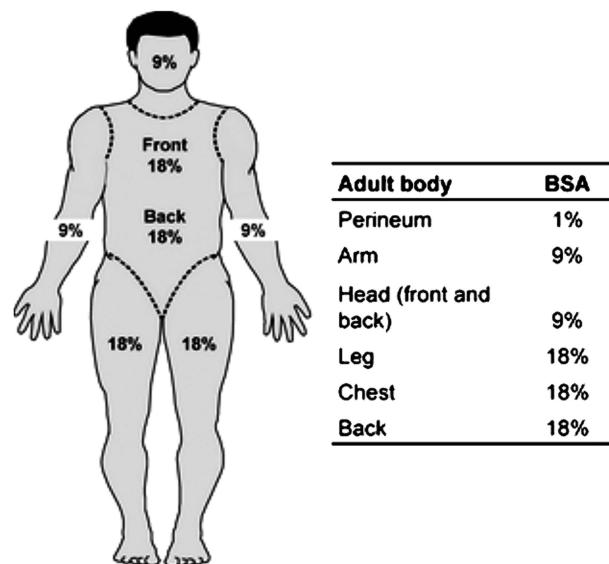


Figure 1 Body surface area.

The rating of this domain should take into account the following comments:

A *persistent cough* is scored if linked to bronchial involvement ascertained by either HRCT (bronchial thickening or dilation) or pulmonary function tests (PFTs) (obstructive syndrome) and not due to active infection or tobacco use. Long-lasting (more than 12 months) persistent but stable cough more likely due to damage than activity should be scored as 0. Persistent cough only due to bronchial dryness should be scored as 0.

To be more precise and clear we modified the wording of the low disease activity level and changed 'or' by 'due to' bronchial involvement.

Interstitial lung disease, if suspected, should have been ascertained at least once in the patient history by HRCT by the presence of mainly ground glass aspect (rather than honeycombing aspects). HRCT should be repeated if symptoms, or radiological or lung function test worsening has occurred. For follow-up, classification is made either on lung function test and/or shortness of breath.

Shortness of breath resulting in slight limitation of physical activity: patient being comfortable at rest, but for whom ordinary physical activity results in fatigue, palpitation or dyspnoea, is classified as NYHA stage II and is scored as moderate activity. If limitation is more marked with symptoms present for ordinary activity and/or at rest (NYHA III or IV), activity is scored as high.

Shortness of breath due to another cause, such as tobacco-related chronic bronchitis, cardiac insufficiency, arterial pulmonary embolism or infection) should be scored as 0. Also, other autoimmune diseases associated with interstitial lung disease should have been excluded.

Non-evolving long-lasting (more than 12 months) interstitial lung disease thought to be due to damage rather than activity should be scored as 0.

Renal domain

Domain	Activity level	Description
Renal <i>Rate as 'No activity' stable long-lasting features related to damage and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first</i>	No=0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis or long-lasting stable proteinuria due to damage
	Low=5	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 mL/min)
	Moderate=10	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High=15	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day, or haematuria or renal failure (GFR <60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement
GFR, glomerular filtration rate.		

The rating of this domain should take into account the following comments:

If a renal biopsy has been carried out, this should be used to rate activity. If not, then proteinuria, haematuria, urinary pH and blood tests should be used.

Renal tubular acidosis is defined by the presence of hyperchloraemia and low serum bicarbonate level both outside the normal laboratory value.

Renal involvement that is thought to be due to causes other than SS, for example, nephro-angiosclerosis, diabetes, renal involvement associated with endocrine diseases, drugs, viral infections, haematological diseases or other systemic diseases, should be scored as 0.

Long-lasting (more than 12 months) non-evolving renal involvement thought to be due to damage rather than activity should be scored as 0.

Muscular domain

Domain	Activity level	Description
Muscular <i>Exclusion of weakness due to corticosteroids</i>	No=0	Absence of currently active muscular involvement
	Low=6	Mild active myositis shown by abnormal EMG, MRI* or biopsy with no weakness and creatine kinase ($N \leq CK \leq 2N$)
	Moderate=12	Moderately active myositis proven by abnormal EMG, MRI* or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase ($2N < CK \leq 4N$),
	High=18	Highly active myositis shown by abnormal EMG, MRI* or biopsy with weakness (deficit $\leq 3/5$) or elevated creatine kinase ($>4N$)
*We decided to add this item not included in the initial version since the value of this examination for the diagnosis of myositis was not clear until recently. EMG, electromyogram.		

The rating of this domain should take into account the following comments:

Diagnosis of myositis should be made on the association of clinical symptoms (muscular pain or weakness) and/or CK elevation and either muscular involvement confirmed by needle detection on EMG, by diffuse inflammation on MRI and/or active myositis on biopsy. Therefore, having one positive examination among EMG, MRI or biopsy is mandatory, but all are not necessary.

EMG should be performed by an accredited neuro-physiologist. MRI evidence myositis with diffuse inflammation has been added to the definition of muscular domain, due to the recognised value of this examination for that purpose. Muscle biopsy is not mandatory in the definition of the activity levels of the domain, but advised in case of uncertainty on the diagnosis. A new biopsy is not mandatory in case of recurrence of the same symptoms with creatine kinase elevation and a previous biopsy showing inflammatory myositis.

Patients having only muscular pain but no muscle weakness and normal creatine kinase level should be scored as low activity; active myositis is proven either by abnormal EMG, MRI or biopsy.

Non-autoimmune causes (infection, statins and other drugs or toxics, etc) should be excluded. Muscle weakness or involvement that is thought to be due to causes other than SS, such as fibromyalgia, corticosteroids, statins or other classified auto-immune disease should be scored as 0.

PNS domain

Domain	Activity level	Description
PNS <i>Rate as 'No activity' stable long-lasting features related to damage or PNS involvement not related to the disease</i>	No=0	Absence of currently active PNS involvement
	Low=5	Mild active PNS involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia <i>*Proven small fibre neuropathy</i>
	Moderate=10	Moderately active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIPD) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High=15	Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit $\leq 3/5$, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIPD) with severe functional impairment: motor deficit $\leq 3/5$ or severe ataxia
*We decided to add this item not included in the initial version since the link between this entity and SS was not clear until recently. CIPD, chronic inflammatory demyelinating polyneuropathy; NCS, nerve conduction study.		

The rating of this domain should take into account the following comments:

For all peripheral neuropathy (except cranial nerve neuropathy and small fibre neuropathy), peripheral neurological involvement should have been ascertained by NCS at least once. The diagnosis of patients with peripheral neuropathy requires exhaustive evaluation of signs and symptoms, followed by confirmation by electrodiagnostic studies, which are useful in establishing the type of neuropathy and whether it is primarily demyelinating or axonal.

Some types of neuropathy may require additional diagnostic tests:

- ▶ Proximal demyelinating neuropathy: elevated cerebrospinal fluid protein level and/or sensory evoked potentials.
- ▶ Small fibre neuropathy should have been ascertained by a cutaneous biopsy, and/or altered or absent

laser-evoked potentials and/or abnormal quantitative sensory testing to thermal stimuli and/or abnormal sympathetic sensory testing.

For muscular testing, grade 3/5 means that the patient holds test position against gravity with no added pressure, but not against external pressure. If the motor deficit is grade 3 or less, activity should be scored as high.

Peripheral neuropathy that is thought to be due to causes other than SS, such as diabetes, or due to metabolic or toxic causes, or that are inherited, should be scored as 0.

Long-lasting (more than 12 months) non-evolving neurological involvement thought to be due to damage rather than activity should be scored as 0.

Central nervous system domain

Domain	Activity level	Description
CNS <i>Rate as 'No activity' stable long-lasting features related to damage or CNS involvement not related to the disease</i>	No=0	Absence of currently active CNS involvement
	Moderate=10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High=15	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit

The rating of this domain should take into account the following comments:

CNS events (except lymphocytic meningitis) must be supported by abnormalities on MRI able to explain the symptoms presented by the patient, and different from what could be observed in a same age subject, according to an experienced neuroradiologist or neurologist. Optic neuritis should be confirmed either by visual-evoked potentials or MRI. Cerebrovascular events or white matter lesions that are likely due to atherosclerosis or cardiac embolism, infectious disease, or other autoimmune disease, should be scored as 0.

In case of a certain diagnosis of MS by an experienced neurologist or fulfilment of the 2010 McDonald MS diagnostic criteria,¹³ involvement should be considered as MS and should not be scored in the ESSDAI.

Long-lasting (more than 12 months) non-evolving neurological involvement thought to be due to damage rather than activity should be scored as 0.

Haematological domain

Domain	Activity level	Description
Haematological <i>For anaemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered. Exclusion of vitamin or iron deficiency, drug-induced cytopenia</i>	No=0	Absence of autoimmune cytopenia
	Low=2	Cytopenia of autoimmune origin with neutropenia ($1000 < \text{neutrophils} < 1500/\text{mm}^3$), and/or anaemia ($10 < \text{haemoglobin} < 12 \text{ g/dL}$), and/or thrombocytopenia ($100\,000 < \text{platelets} < 150\,000/\text{mm}^3$) Or lymphopenia ($500 < \text{lymphocytes} < 1000/\text{mm}^3$)
	Moderate=4	Cytopenia of autoimmune origin with neutropenia ($500 \leq \text{neutrophils} \leq 1000/\text{mm}^3$), and/or anaemia ($8 \leq \text{haemoglobin} \leq 10 \text{ g/dL}$), and/or thrombocytopenia ($50\,000 \leq \text{platelets} \leq 100\,000/\text{mm}^3$) Or lymphopenia ($\leq 500/\text{mm}^3$)
	High=6	Cytopenia of autoimmune origin with neutropenia ($\text{neutrophils} < 500/\text{mm}^3$), and/or anaemia ($\text{haemoglobin} < 8 \text{ g/dL}$) and/or thrombocytopenia ($\text{platelets} < 50\,000/\text{mm}^3$)

The rating of this domain should take into account the following comments:

Cytopenias that are thought to be due to causes other than SS should be scored as 0.

- ▶ Cytopenia due to drug-induced toxicity, viral infections or haematological disorder other than auto-immunity or lymphoma;
- ▶ Anaemia due to iron or vitamin deficiency;
- ▶ Neutropenia of ethnic origin or due to drug associated agranulocytosis;
- ▶ Thrombocytopenia linked to hypersplenism.

Other causes of autoimmune cytopenia should have been discarded.

Biological domain

Domain	Activity level	Description
Biological	No=0	Absence of any of the following biological feature
	Low=1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate=2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level $> 20 \text{ g/L}$, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level ($< 5 \text{ g/L}$)

The rating of this domain should take into account the following comments:

If both IgG and gammaglobulin levels are available, take the highest value and continue to use the same test in the same patient for longitudinal examination.

A clonal component can be detected by serum electrophoresis, serum or urine immunofixation or by an abnormal ratio of free light chains in the serum.

The biological presence of cryoglobulinemia should be taken into account even if there is no clinical sign, even in the case of low cryocrit levels ($< 1\%$). Clinical signs related to cryoglobulinemia should be additionally scored in each domain.

CONCLUSION

Since its development, the ESSDAI has been frequently used in primary SS clinical studies. The ESSDAI is now in use as a gold standard, as the SLEDAI or BILAG is in lupus,^{14 15} to measure systemic disease activity in clinical and biological studies in SS that aim at evaluating new biomarkers of activity.^{16–19} It has been shown to correlate with B-cell biomarkers such as $\beta 2$ microglobulin, serum free light chains of immunoglobulins,^{5 20} the cytokine BAFF⁶ and to be associated with the risk of lymphoma.^{6 21}

In addition, ESSDAI has started to be used as an outcome measure in RCTs in SS, and even as the primary outcome measure in currently ongoing RCTs. Recently, the definition of disease activity levels and thresholds of minimal clinically important improvement (MCII) have been recently proposed for that tool: a moderately active disease being defined as an ESSDAI ≥ 5 and an MCII as a decrease of at least 3 points.²² These cut-offs have started to be used, respectively, as entry criteria and primary end points for RCTs (testing tocilizumab [NCT01782235] or abatacept [NCT02067910]). In this setting, enhancing the accuracy and the reliability of disease activity scoring to correctly classify patients at study entry but also at final evaluation is a crucial point to determine the efficacy of the drug under investigation.

Finally, the detailed definitions given in this paper on the way to rate each of the ESSDAI domains will be useful in future RCTs as well as in clinical practice. We hope it will improve the accuracy of clinical trials data and help to demonstrate the effectiveness of future treatment in patients with primary SS.

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